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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,868	10/24/2001	Rifat Pamukcu	P-168-1	8300
7590	03/24/2004			
OSI PHARMACEUTICALS, INC. 58 SOUTH SERVICE ROAD SUITE 110 MELVILLE, NY 11747				
EXAMINER OWENS JR, HOWARD V				
ART UNIT 1623		PAPER NUMBER		

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/003,868

Applicant(s)

PAMUKCU ET AL.

Examiner

Howard V Owens

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**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --****Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 01 March 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-6 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                                    |

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### Response to Arguments

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/1/2004 has been entered.

### **35 U.S.C. § 103**

Applicant's arguments filed 3/1/04 have been fully considered but they are not persuasive. The rejection of claims 1-6 under 35 U.S.C. 103(a) as being unpatentable over Nishi et al., U.S. Patent No. 5, 998,437 in combination with Taylor et al., U.S. Patent No. 4,950,680 and Earnest et al., Journal of Cellular Biochemistry, supplement 161:pp. 156-166 and Fang et al., Journal of Biological Chemistry, vol.272(23), pp. 14860-14866 is maintained for the reasons of record.

Claims 1-6 are drawn to a method of treating a mammal having a precancerous lesion, inhibiting neoplastic cells and regulating apoptosis comprising administering a pharmacologically effective amount of a fused pyrimidine compound of formula 1.

Nishi et al. teach fused pyridine inhibitors analogous to those set forth in the instant claims (see abstract and columns 2-16) and teach that these derivatives are selective inhibitors of cGMP phosphodiesterase (col. 1, line 41 - col.2, line 14). However, Nishi does not teach the treatment of precancerous lesions, the inhibition of neoplastic cells nor the regulation of apoptosis as uses for the compounds.

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Fang et al. teach that a cGMP-phosphodiesterase inhibitor can induce apoptosis in cardiac myocytes (p. 14863) which adequately bridges the nexus between the use of compounds which have an inhibitory effect on cGMP-PDE as inducers of apoptosis.

Taylor et al. teach (col.3, line 43 - col. 4, line 55 and col. 5, lines 15-20) that tumor metastasis is enhanced by tumor cell interactions with platelets and that agents which block or prevent tumor cell-platelet interaction and aggregation such as inhibitors of TXA<sub>2</sub> synthetase and phosphodiesterase have antimetastatic effects; moreover, Earnest et al. teach that phosphodiesterases and cyclic cGMP kinases (and inhibitors thereof) may be central to cancer initiation and promotion (see abstract and pp. 157-159) which adequately bridges the nexus between the differences in the prior art and the invention as claimed.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the examiner set forth the teachings of Nishi et al. to establish the fact that applicant's compounds although not claimed as such nor set forth in the instant specification are in fact recognized as phosphodiesterase inhibitors in the prior art. Applicant can not discount the teachings of Nishi (when the same compounds of Nishi deemed as cGMP phosphodiesterase inhibitors are set forth in the instant invention) and simultaneously argue that prior art references which do not recite cGMP phosphodiesterase inhibition fail to support a basis of obviousness for the instant invention. If applicant admits that only prior art references which recite cGMP are appropriate, than Nishi is appropriate; additionally, applicant's specification is silent with regard to either cGMP/ cAMP phosphodiesterase activity and differentiation with respect to this compound in relation to anti-tumor or apoptotic activity, thus the issue of "impermissible hindsight reasoning" with regard to the use of Nishi et al. is moot since these teachings were gleaned outside of applicant's teachings. Moreover, if Nishi specifically mentioned or cited neoplasia as being affected by cGMP phosphodiesterase inhibitors than the claims would be rejected under 35 U.S.C. 102(b), not 103(a). All the elements of the claims need not be expressly taught in one reference to provide a basis of obviousness. The teachings of Taylor and Earnest were set forth to show the link in the prior art between phosphodiesterase inhibitors and tumor growth. Taylor teaches the use of phosphodiesterase inhibitors as agents which block or prevent tumor cell-platelet interaction and aggregation. Applicant's assertion that the teachings of Taylor are restricted to cAMP phosphodiesterase inhibitors is not convincing. Applicant has chosen the lone Figure correlating cAMP and phosphodiesterase to define the teachings as a whole. The bulk of Taylor teaches phosphodiesterase inhibitors broadly

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as agents which block or prevent tumor cell-platelet interaction and aggregation. No where in either Taylor or Earnest is it taught that the invention as a whole is limited to "PD1" type inhibitors as applicant asserts. Moreover, one of skill in the art would have a reasonable expectation of success in the use of an agent or compound which is effective against tumors in the treatment of tumor growth for primary tumors. Earnest like Taylor has provided sufficient motivation for the nexus of phosphodiesterase inhibitors as effectors of tumor growth, as it teaches that "phosphodiesterases ..... may be central to cancer initiation and promotion".

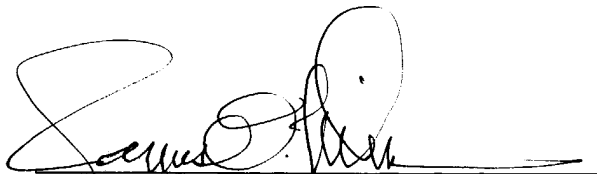
The examiner maintains the position that a person of ordinary skill in the art would have been motivated to use the fused pyrimidines of formula I to treat precancerous lesions, inhibit neoplastic cells or regulate apoptosis as the prior art teaches that these compounds as inhibitors of TXA2 synthetase and phosphodiesterase have an anti metastatic effect through the inhibition of tumor cell induced platelet aggregation; moreover, that one of skill in the art would have a reasonable expectation of success in the treatment of precancerous lesions with the fused pyrimidine compounds of the invention, or any compound for that matter which inhibits cGMP phosphodiesterase as the inhibition of this enzyme has been shown in the prior art to disrupt the cellular cascade from which certain neoplasms are formed.

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All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Howard V. Owens  
Patent Examiner  
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A handwritten signature in black ink, appearing to read 'James O. Wilson', is written over a horizontal line.

James O. Wilson  
Supervisory Patent Examiner  
Technology Center 1600

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Howard Owens whose telephone number is (571) 272-0658. The examiner can normally be reached on Mon.-Fri. from 8:30 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the Supervisory Patent Examiner signing this action, James O. Wilson can be reached on (571) 272 - 0661.